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Atty. Docket WEG-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants:	Edwin Wegman, et al.
Serial No.:	08/757,904
Filed:	November 27, 1996 (as a File Wrapper Continuation of: Serial No. 08/356,112 filed December 15, 1994)
For:	Reduction of Adipose Tissue
Examiner:	Ms. Jean C. Witz
GAU:	1651

APPELLANTS' BRIEF

This is an appeal from the decision of the Examiner dated November 10, 1997 (Paper No. 19) rejecting claims 1-21.

(1) REAL PARTY IN INTEREST

The real party in interest is applicants' assignee, Advance Biofactures of Curacao, N.V., Industrial Park, Brievengat, Curacao, Netherlands Antilles. This party is listed as the assignee in the assignment recorded in the Patent Office on December 15, 1994 at Reel/Frame 7283/0110.

(2) RELATED APPEALS AND INTERFERENCES

Applicants' attorney is not aware of any related appeals or interferences.

(3) STATUS OF CLAIMS

All of the claims, 1-21 inclusive, stand finally rejected.

Claims 1, 16 and 20 are independent claims. All others depend, directly or indirectly, on one of these.

The original application as filed contained claims 1-15. Claims 16-21 were added during prosecution. Claims 1 and 16 were amended during prosecution.

A clean copy of the appealed claims is presented in the Appendix to this brief.

(4) STATUS OF AMENDMENTS

No amendments were filed after the Final Office Action, dated November 10, 1997, from which this appeal is taken.

(5) SUMMARY OF THE INVENTION

The invention provides an alternative to surgical liposuction (Specification, page 2, lines 10-13; page 7, lines 4-5). For cosmetic purposes adipose tissue at selected locations in the body is disrupted and reduced in amount by introducing into said tissue the enzyme collagenase or collagenase plus another proteinase enzyme (Specification, page 2, lines 13-19; all of pages 7 through 23). Fat (the principal component of adipose tissue) released by action of the collagenase is metabolized by the

body whereby the amount of fat and hence of adipose tissue at the selected location is reduced (Specification, page 6, line 23, through page 7, line 1). The amount of reduction of the adipose tissue from its original volume may range from 25% to 75% and higher (Specification, page 2, lines 17-19; page 15, lines 1-20).

(6) ISSUES

Are claims 1-21 unpatentable under 35 U.S.C. § 103 over Lee et al., U.S. 5,424,208, combined with Guidicelli et al., Biochimica et Biophysica Acta, 450 (1976) 358-366?

(7) GROUPING OF CLAIMS

The claims of group 1-21 do not stand or fall together. Claims 19 and 21 as a group are believed to be separately patentable from the other claims. The reasons are stated at the end of the Argument section of this brief.

(8) ARGUMENT

Applicants' invention is an in vivo method that reduces the amount of adipose tissue at selected locations in the body by causing actual removal of adipose tissue from said locations. The active agents are two: (a) collagenase introduced from outside the body, that causes release of fat from the tissue, and (b) biological processes within the body that metabolize residue from the adipose tissue

including released fat. Thus fat is removed from the location where the collagenase was introduced. As shown in the experimental work detailed at pages 7 through 23 of the specification, using Zucker rats which have four well-defined subcutaneous fat pads, disruption of the adipose tissue ranged from mild to complete (Grades I to IV) depending on dosage and manner of injection. In Experiment E at page 15, lines 1-20, weight losses from the fat pads were 41%, 25% and 18%, averaging 28%; i.e., on average, over one-fourth of the substance of a fat pad had disappeared from that location.

The rejection, under 35 U.S.C. § 103, is on Lee et al., combined with Guidicelli, et al.

Lee et al. use collagenase plus chymopapain to digest connective tissue. Their principal interest is in isolating in the laboratory microvessel cells embedded in such tissues. They also state that their collagenase-containing compositions can be used for the treatment of burns or ulcers, for intervertebral discolysis, for assisting in ophthalmic surgery, for the treatment of submucous fibrosis, for the treatment of Peyronie's disease, for the local enzymatic treatment of atherosclerotic plaques, and in the treatment and prevention of the development of familiar

amyloidotic polyneuropathy (FAP) (column 7, line 67, through column 8, line 7).

The present invention cannot be derived from Lee et al. They are not interested in bodily adipose tissue except as the raw material source of microvessel cells (used to coat implants such as artificial blood vessels and prosthetic devices). Although they applied their enzyme mixture in vitro to fat that had been liposuctioned out of the body, it did not occur to Lee et al. and Lee et al. do not suggest to use their mixture in vivo as an alternative to liposuction. Nor is it obvious to do so.

What happens in the body to fat released by applicants' invention is quite different from what happens to fat released in Lee et al.'s laboratory. In the latter, adipose tissue obtained by liposuction is treated with collagenase plus papain. Microvessel cells and adipocytes (fat cells) are released. The adipocytes survive intact. Upon centrifuging, the adipocytes and supernatant are pipetted off from the pellet of microvessel cells (Column 8, lines 45-51; column 11, lines 22-27).

There is nothing in Lee et al. to suggest that their enzymes be used to digest the connective tissue of adipose tissue in vivo, or if that were done, that a substantial

amount of the adipose tissue would disappear from the site. In applicants' invention, the body itself removes released fat from the selected location of treatment, resulting in less fatty material there. This disappearance of fat from the selected locations provides the desired cosmetic result. It could not be predicted from Lee et al.

Though Lee et al. state that their collagenase plus chymopapain can be utilized to digest connective tissue, and administered in vivo for certain maladies, this in no way suggests applicants' teaching of reducing the amount of fat at selected locations in the body. This is an essential and unobvious result in applicants' method.

The secondary reference, Guidicelli et al., prepared fat cells by digestion of adipose tissue with collagenase plus trypsin, using the method published by Fain and Loken (1969). This adds nothing to the teaching of Lee et al. As in Lee et al., the fat cells (adipocytes) survived intact (page 359, third paragraph under Materials and Methods).

Turning now to the Examiner's positions, as stated in the final rejection of November 10, 1997:

On page 3, second paragraph, the Examiner says:

> Applicants' characterization of both the claim language and the Lee et al. reference is much too narrow. The claim language recites that to reduce adipose tissue at a selected site in the body one

> administers to that adipose tissue collagenase or collagenase in conjunction with other proteinases so that the adipose tissue at the site is reduced. This method may be practical for cosmetic purposes. This is all that is required of the claimed method. (emphasis added)

This totally ignores the recitations in the last half of the independent claims 1, 16 and 20, wherein the body metabolizes released fat whereby the amount of adipose tissue at said selected locations is reduced. The Examiner disregards the experimental data showing that when the collagenase disrupts the adipose tissue, a significant portion of the tissue actually disappears from the site, the clear meaning of reduced in this patent application.

This disregard of the data is again shown in the word play of the last paragraph of page 4. A definition of tissue is stretched for the purpose of holding that as soon as the dissolution of the connective tissue matrix occurs, no adipose tissue exists and hence the amount of tissue has been reduced. Even taking this concept of tissue, the claims still recite that the body metabolizes the released fat.

Finally, the same line of reasoning culminates in the Office Action at lines 11 and 12 of page 5:

> As for the claims, what happens to the intact and ruptured adipocytes after the administration is immaterial to the claimed invention.

How can that be immaterial to the claimed invention when it is part of the claimed invention? It is a vital part. Again, the Examiner is ignoring the fact that reducing the amount of adipose tissue at the selected location includes its disposal.

The Examiner has failed to heed the axiom that claims are to be read in their entirety, giving words their plain meaning, and if there is any question, they must be read in light of the specification. The experimental work reported in applicants' specification teaches that the word reduced in the claims means that at least some of the adipose tissue disappears from the selected location, i.e., where collagenase was introduced.

In the first complete paragraph of page 4 of the Office Action, the first four sentences correctly describe the teachings of Lee et al. and Guidicelli et al. with respect to <u>in vitro</u> procedures.

The fifth sentence states: Further, it is expected that in the resulting hydrolysis of the matrix that fat

cells will be damaged and disrupted, thereby releasing the oil within. Expected by whom? This is contrary to the fat cells surviving intact in both references. The expectation of the Examiner is derived entirely from applicants' experimental data showing that in vivo there is damage and disruption of fat cells and release of oil. The last sentence of the paragraph says: There is clearly no effect of the collagenase on the fat contained in the adipocyte. Applicants do not assert that collagenase has an effect on the fat or oil contained in adipocytes. Rather, as recited in the claims, the collagenase digests the connective tissue, and the body metabolizes released fat.

The last paragraph of page 4 of the Office Action has been discussed earlier. The last sentence thereof states that it is clear from the disclosure of Lee and Guidicelli that the effects of collagenase on adipose tissue result in the disruption of the tissue into cells and cell debris. Neither reference shows any cell debris.

At page 5, first paragraph, it is held that the term for cosmetic purposes fails to define the claims over the art. There is nothing in the references to suggest that their enzyme mixtures be considered for cosmetic purposes. Again, the Examiner relies on the position that digestion of

the connective tissue component alone constitutes reduction in the amount of adipose tissue, ignoring the claim recitations and teachings that reducing is accomplished by metabolizing fat.

Chemical liposuction is a short-hand expression used by applicants' attorney during prosecution. It has never been argued that the invention is the equivalent of liposuction, bur rather an alternative. Nor have any comparisons of safety been made. The Examiner says that liposuction means removal of fat from the body. True. But in applicants' claimed invention, fat is removed from the treated location, which is the cosmetic intent, by the body s metabolism subsequent to the injection of collagenase. The amount of actual material that is removed may be 25% or more.

The paragraph bridging pages 5 and 6 reveals the Examiner's insistence that the only thing that matters is the digestion of connective tissue, not what happens as a consequence. There is no way to predict from the prior art, with any degree of certainty or expectation of success, the invention claimed.

As mentioned before, it is noteworthy that Lee at al. disclosed the administration of their enzymes to a human or

animal for the treatment of seven conditions, but did not include reducing the amount of subcutaneous fat. They actually carried out surgical liposuction to obtain adipose tissue, yet the idea did not occur to them. The Examiner notes at page 4, lines 5-6, of the Office Action that Guidicelli et al. (1976) disclosed that it is conventional to use collagenase and trypsin for the purpose of digesting and isolating adipocytes. Guidicelli et al. referred to Rodbell (1964) and Fain and Loken (1969) for this. So the information has been available for at least 30 years. During the same period and earlier, a large number of investigators have utilized collagenase for a great variety of purposes. None thought of applicants' invention. The field of liposuction has vastly expanded over the past 15 or more years along with increasing reports of deaths and serious morbidity. Yet applicants' invention has not occurred to those working in the field of liposuction, despite the ready availability of collagenase and its <u>in vivo</u> use for other purposes.

* * * * *

As stated in the Grouping of Claims section above, claims 19 and 21 are considered separately patentable from the other claims. This is because they recite numerical

limits on the amount of reduction of adipose tissue at the selected locations, viz, from 25% to 75%, and at least 25%, respectively.

Lee et al. and Guidicelli et al. worked with adipose tissue outside the body. Lee et al. obtained theirs by liposuction. Guidicelli et al. obtained theirs from patients undergoing abdominal surgery.

Not only was applicants' invention of reducing the amount of adipose tissue at selected locations in the body unobvious, it was also impossible to predict, from the in vitro experiments of the references, the amount of such reductions.

Respectfully submitted,

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APPENDIX

THE APPEALED CLAIMS

1. A method of reducing for cosmetic purposes the amount of adipose tissue at selected locations in the body which comprises introducing into said tissue effective amounts of collagenase or collagenase plus another proteinase, said adipose tissue comprising connective tissue and fat, said collagenase digesting said connective tissue, and the body metabolizing fat released from said adipose tissue whereby the amount of adipose tissue at said selected locations is reduced for cosmetic purposes.

2. A method according to claim 1 wherein said adipose tissue is subcutaneous.

3. A method according to claim 1 wherein said another proteinase is a cysteine proteinase.

4. A method according to claim 3 wherein said cysteine proteinase is clostripain.

5. A method according to claim 1 wherein said another proteinase is a serine proteinase.

6. A method according to claim 5 wherein said serine proteinase is trypsin.

7. A method according to claim 5 wherein said serine proteinase is chymotrypsin.

8. A method according to claim 1 wherein said collagenase or collagenase plus another proteinase in a pharmaceutically acceptable carrier is injected into said adipose tissue.

9. A method according to claim 8 wherein a solution of collagenase or collagenase plus another proteinase in a liquid pharmaceutically acceptable carrier is injected.

10. A method according to claim 9 wherein said carrier is aqueous.

11. A method according to claim 9 wherein said adipose tissue is subcutaneous and said solution is injected percutaneously at a multiplicity of closely spaced sites.

12. A method according to claim 1 wherein the collagenase is introduced in the amount of from about 5 to about 150 ABC units collagenase per gram of adipose tissue treated.

13. A method according to claim 12 wherein said amount of collagenase is from about 10 to about 100 ABC units collagenase per gram of adipose tissue treated.

14. A method according to claim 1 wherein said another proteinase is introduced in the amount of from about 0 to about 350 FFC units proteinase activity per gram of adipose tissue treated.

15. A method according to claim 12 wherein the collagenase is introduced in a liquid pharmaceutically acceptable carrier in a concentration of from 50 to about 5,000 ABC units per mL.

16. A method of reducing for cosmetic purposes the amount of subcutaneous adipose tissue at selected locations in a human body, which comprises introducing into said tissue about 5 to about 150 ABC units of collagenase per gram of adipose tissue treated, the collagenase dissolving adipose tissue s connective tissue, and the body metabolizing fat released by said digested connective tissue, leaving said selected location with a reduced amount of said adipose tissue.

17. The method according to claim 16, wherein said collagenase is injected percutaneously at a multiplicity of closely spaced sites.

18. The method according to claim 16, wherein said amount of collagenase is from about 10 to about 100 ABC units of collagenase per gram of adipose tissue treated.

19. The method according to claim 16, wherein reduction of said tissue from its original volume ranges from 25% to 75%.

20. A method of reducing for cosmetic purposes the amount of adipose tissue at selected locations in the body which comprises introducing into said tissue effective amounts of collagenase or collagenase plus another proteinase, said adipose tissue comprising connective tissue and fat, said collagenase digesting said connective tissue, and the body removing from said selected locations fat released from said adipose tissue whereby the amount of adipose tissue at said selected locations is reduced for cosmetic purposes.

21. The method according to claim 20, wherein said adipose tissue is reduced from its original volume by at least 25%.